Remarks/Arguments

The foregoing amendments to the claims are of formal nature, and do not add new matter. Claims 119-138 were pending in this application and were rejected on various grounds. All pending claims have been amended to remove references to "Figures". Claims 119-123 have been amended with the functional recitation "wherein said polypeptide stimulates cardiac hypertrophy," support for which is found in the instant specification in Example 148. Further, new claims 138-143 which recite the functional recitation "wherein, said encoded polypeptide induces chondrocyte redifferentiation" have been added, support for which is also found in the instant specification in Example 159. Claims 128 and 132-134 have been canceled without prejudice or disclaimer. Accordingly, Claims 119-127, 129-131, 135-143 are currently pending in this application and rejections to these claims are respectfully traversed.

Specification

The disclosure was objected to by the Examiner as containing "embedded hyperlink and/or other form of browser-executable code." The foregoing amendment to the specification which deleted all embedded hyperlinks, is believed to overcome the present objections. Further, any minor errors have been amended.

Accordingly, Applicants believe that all objections to the specification has been overcome.

Claim Rejections – 35 U.S.C. § 101

Claims 137 was rejected under 35 U.S.C. §101, for not sufficiently distinguishing over cells that exist naturally.

The claim has been amended to recite "isolated" as recommended by the Examiner to overcome this rejection and accordingly this rejection should be withdrawn.

Claim Rejections – 35 U.S.C. § 112, second paragraph

Claims 119-124, 128 and 132-134 were rejected under 35 U.S.C. §112, second paragraph for being indefinite. The Examiner found the recitation of part (d) of the claims indefinite.

Further, claims 132-134 were indefinite for reciting "hybridizes" without recitation of the conditions used.

Without acquiescing to the propriety of this rejection and without limitations to pursuing this subject matter in future applications, merely to expedite prosecution in this case, Applicants have canceled references to part (d) in the pending claims and further, have canceled claims 132-134 without prejudice or disclaimer. Accordingly, this rejection should be withdrawn.

Claim Rejections - 35 U.S.C. § 112, first paragraph -written description

Claims 119-123 are rejected under 35 U.S.C. 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time of filing.

As will be discussed below, specific utilities have now been asserted for the presently pending claims that recite functional recitations "wherein said polypeptide stimulates cardiac hypertrophy" and "wherein said encoded polypeptide induces chondrocyte redifferentiation." Since the claims are drawn to a genus of nucleotides defined both by sequence and functional identity, it would have been obvious to one skilled in the art at the effective priority date, in view of Applicant's possession of the nucleic acid of SEQ ID NO:386 and the PRO1312 sequence (SEQ ID NO:387), that the Applicant possessed these obvious variations and adaptations of SEQ ID NO:387 at the time of filing, as further discussed below. Hence, Applicants request that the present rejection be reconsidered and withdrawn.

Claim Rejections - 35 U.S.C. § 112, first paragraph -enablement

Claims 119-123, 131-138 are rejected under 35 U.S.C. §112, first paragraph for lack of enablement. The Examiner objected to the disclosure for lack of evidence for the claimed biological materials required for practicing the claimed invention, for allegedly, not being known and readily available to the public or obtainable by a repeatable method set forth in the specification.

Applicants submit that the specification contains information regarding ATCC accession no. 203132 which was deposited August 18, 1998 (also called DNA 61873-1574) on page 565,

line 35. This deposit was made under the provisions of the Budapest Treaty. Applicants further submit amendments to the specification regarding the ATCC deposit incorporating the requisite assurances that "all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the pertinent U.S. patent." Accordingly, Applicants request that this rejection be withdrawn.

Claim Rejections – 35 U.S.C. § 112, first paragraph-enablement

Claims 119-123 and 132-138 are rejected under 35 U.S.C. §112, first paragraph for failing to adequately teach how to make and/or use the instant invention. The Examiner alleges that the specification does not enable any person skilled in the art for DNAs that are at least 80% identical. For the reasons outlined below, Applicants respectfully disagree.

Initially, Applicants submit that the instant claims do not have utility based on "homology" and hence the articles Burgess *et al.*, Lazar *et al.*, Schwartz *et al.* and Lin *et al.* are not appropriate citations in this instance. Instead, utility is based on positive results of obtained in the "stimulation of heart neonatal hypertrophy assay (Example 148 on page 523) and the 'chondrocyte redifferentiation' assay (Example 159) and these functional recitations are now recited in the instant claims.

PRO1312 polypeptides have utility based on the stimulation of neonatal heart hypertrophy assay

Hypertrophy of the heart is usually associated with a failing heart or heart remodeling. It is characterized by an increase in size and content of contractile protein of individual cardiac muscle cells. Cardiac hypertrophy is activated by both mechanical and hormonal stimuli and, within certain limits, enables the heart to adapt to the demands for increased cardiac output or injury. Identification of factors which mediate the onset of various phases of cardiac hypertrophy, including heart failure is a major pursuit in cardiac biology and medicine (Chien, KR, Science, (1993) 260:916-7; Katz, AM, Circ. J. (2002), 66: 225-231). Thus, identification of factors that can induce cardiac myocyte hypertrophy are useful in the development of new therapeutic strategies to inhibit pathophysiological cardiac growth.

The hypertrophy assay disclosed in the present application, and its modifications are widely used for identifying factors that cause hypertrophy of the heart (for example; see Pennica *et al.*, P.N.A.S., (1995), 92: 1142-46; and, Lai *et al.*, Am. J. Physiol. (1996) 271: H2197-208). Usually, ventricular cardiac myocytes, isolated either from neonatal or adult rats, are used in this assay. Test factors are added to myocyte cells on day 2, the cells are allowed to grow and then, are fixed and stained on day 5. A hypertrophy score is assigned to cells showing growth enhancement compared to control cells on the following basis: 0, for cells showing no growth enhancement; 1.0, for cells showing moderate growth enhancement; and, 2.0, for cells showing large growth enhancement. The specification indicates that any degree of growth enhancement as compared to the negative control cells was considered positive in this assay.

PRO1312 showed positive growth enhancement in this assay and thus, PRO1312 and its antibodies have utility in the development of new therapeutic drugs to inhibit pathophysiological cardiac growth. One skilled in the art would readily understand and appreciate this utility, and know how to make and use the claimed invention based on the general knowledge in the art and the disclosure of the present application.

PRO1312 polypeptides also have utility based on results in chondrocyte redifferentiation assay

Applicants further rely on the chondrocyte redifferentiation assay (Example 159) for support of patentable utility.

It was well known at the effective filing date of the present application that chondrocytes play a key role in the synthesis and maintenance of the articular cartilage, which in turn is essential to normal joint function. Unfortunately, compared to many other tissues, articular cartilage essentially lacks the ability to regenerate following injury. One way of achieving cartilage repair, for example in osteoarthritis, is to harvest human articular chrondrocytes (HACs) from non-affected, healthy areas of the joint to be repaired. The HACs are subsequently grown in monolayer cell culture in order to produce sufficient amount of cells to fill the articular defect. Chondrocytes found in healthy joints have a round shape, and express high levels of extracellular matrix molecules, such as aggrecan, type II collagen, and link protein. In contrast, monolayer cultures of chondrocytes produce dedifferentiated fibroblast-like structures, similar to those found in the cartilage of aging and arthritic joints. (See, e.g. Zhang et al., *Experimental Cell*

Research 263:33-42 (2001) – copy enclosed). Accordingly, agents that are capable of inducing chondrocyte proliferation and redifferentiation, as evidenced by proper growth and differentiation of chrondrocytes in monolayer cell cultures, can be used in the treatment of joint diseases using a tissue engineering approach (See, e.g. Schnabel et al., Osteoarthritis and Cartilage, 10(1):62-70 (2002) – copy enclosed). In addition, molecules capable of inducing chondrocyte proliferation and/or redifferentiation are promising drug candidates to repair aging or arthritic joints, for example, in joints where the chondrocytes have been dedifferentiated.

As set forth in M.P.E.P, 2107 II (B) (1), if the applicant has asserted that the claimed invention is useful for any particular practical purpose, and the assertion would be considered credible by a person of ordinary skill in the art, a rejection based on lack of utility should not be imposed. The logic underlying the asserted utility in the present case is not inconsistent with general knowledge in the art, and would be considered credible by a person skilled in the art. It is, of course, always possible that an invention fails on its way of development to a commercial product. Thus, despite recent advances in rational drug design, a large percentage of drug candidates fails, and never makes it into a drug product. However, the USPTO is not the FDA, the law does not require that a product (drug or diagnostic) be currently available to the public in order to satisfy the utility requirement.

Applicants refer to the statement in Example 159, the description of the chondrocyte redifferentiation assay that "A positive result in the assay is obtained when the fluorescence of the PRO polypeptide treated sample is more like that of the positive control than the negative control." Fluorescence determination wherein the readout is compared to controls is well known in the art. Thus, these indica are truly determinative of the proliferation of chondrocyte cells.

Applicants respectfully submit that the specification provides sufficient disclosure to establish a specific, substantial and credible utility for the PRO1312 polypeptide and its encoding nucleic acids. In addition, the instant claims, as amended, (and, as a consequence, those claims dependent from the same) now recite the functional recitation, namely that the encoded polypeptide induces chondrocyte re-differentiation.

Further, since only those variant polypeptides, or polypeptides with 80-99% identity to SEQ ID NO: 387 (and the nucleic acids encoding them) that are positive in the cardiac hypertrophy assay or the chondrocyte redifferentiation assay are encompassed in the instant

claims, and since any person skilled in the art would know how to make mutants of nucleic acid sequence SEQ ID NO: 386 since this technique is routine in the art, the present invention is enabled. Applicants submit that the positions at which the polypeptide sequence is changed/mutated is irrelevant since only those polypeptides which have the function, i.e., are positive in the chondrocyte redifferentiation or cardiac hypertrophy assay as defined in the specification, are encompassed in the instant claims. Therefore, one skilled in the art would know exactly how to make and use the variants of the invention undue experimentation.

In view of the foregoing arguments and submitted evidence, the Examiner is respectfully requested to reconsider and withdraw the present rejections under 35 U.S.C. §112, first paragraph.

Priority

Applicants rely on the " assay (Example) for patentable utility of pending claims 119-123 of this case. This utility was first disclosed in International Application PCT/US99/28313, filed November 30, 1999, priority for which has been claimed in this application. Hence, the present application is at least entitled to an effective filing date of **November 30, 1999** based on the results of the "stimulation of neonatal heart hypertrophy" assay.

Further, Applicants rely on the 'chondrocyte redifferentiation' assay (Example 159) for patentable utility of subject matter relating to new claims 132-136 in this case. This utility was first disclosed in International Application PCT/US00/08439, filed March 30, 2000, priority for which has been claimed in this application. Hence, the present application is at least entitled to an effective filing date of **March 30, 2000** based on results of the 'chondrocyte redifferentiation' assay.

Claim Rejections – 35 USC § 102

Claims 119-123 and 132-138 are rejected under 35 U.S.C. §102(a) as being anticipated by Ruben (WO 99/58660, dated November 18, 1999).

Initially, in view of the cancellation of claims 132-134, these rejections are moot for these claims. While Ruben teaches the sequence of Gene No: 12 similar to SEQ ID NO: 386, Ruben does not teach utilities like neonatal heart hypertrophy or chondrocyte redifferentiation (see pages 31-33 of WO 99/58660) for the nucleic acids as recited in instant claims 119-123. In fact, on

page 32, line 26 onwards, Ruben discloses that many polynucleotide sequences publicly available prior to Ruben's conception are excluded from the scope of Ruben's invention. As will be discussed below based on the attached declaration and exhibit, Applicants had conceived and reduced to practice SEQ ID NO: 386 on **May 29, 1998** which predates the Ruben reference. Therefore Ruben is not prior art and does not anticipate the instantly claimed invention; hence, this rejection should be withdrawn.

Claims 119-123 and 132-138 are rejected under 35 U.S.C. §102(b) as being anticipated by Jacobs (WO 98/32853, dated July 30, 1998).

Applicants have claimed priority to U.S. Provisional Application No. 60/096,960 filed on August 18, 1998 and is entitled to the priority date of **August 18, 1998**. Further, to support this priority claim, as discussed below, Applicants submit that U.S. Provisional Application No. 60/096,960 disclosed subject matter commensurate in scope with the disclosure of the prior art by Jacobs *et al.* Accordingly, the PCT publication WO 98/32853 by Jacobs *et al.* is **102(a) art**, not 102(b) art, against the present application.

U.S. Provisional Application No. 60/096,960 Simply Needs to Disclose What is Disclosed in the Cited Reference to Support the Priority Claim

Applicants respectfully submit that in order to gain support for the priority claim, the provisional application simply needs to provide a disclosure commensurate in scope with the disclosure of the prior art by Jacobs *et al.*

In order to remove a reference as a prior art, "[i]t is sufficient if [the affidavit under Patent Office Rule 131] shows that as much of the claimed invention as is taught in the reference has been reduced to practice by the [patentee] prior to the date of the reference." *In re* Stempel, 241 F.2d 755, 757 (1957). In *In re* Stempel, the patent applicant (Stempel) had claims directed to both (i) a particular genus of chemical compounds (the "generic" claim) and (ii) a single species of chemical compound that was encompassed within that genus (the "species" claim). In support of a rejection under 35 U.S.C. §102, the Examiner cited against the application a prior art reference that disclosed the exact chemical compound recited in the "species" claim. In response

to the rejection, the patent applicant filed a declaration under 37 C.F.R. §1.131 demonstrating that he had made that specific chemical compound prior to the effective date of the cited prior art reference. The Court found the applicant's 37 C.F.R. §1.131 declaration effective for swearing behind the cited reference for purposes of both the "species" claim and the "genus" claim. Specifically, the Court stated in support of its decision that "all the applicant can be required to show is priority with respect to so much of the claimed invention as the reference happens to show. When he has done that he has disposed of the reference." *Id.* at 759.

Furthermore, the Examiner is respectfully directed to *In re* Moore, 170 USPQ 260 (CCPA 1971), where the holding in *In re* Stempel was affirmed. In *In re* Moore, the patent applicant claimed a particular chemical compound in his patent application and the examiner cited against the applicant a prior art reference under 35 U.S.C. §102 rejection which disclosed the compound but did not disclose any specific utility for the compound. The patent applicant filed a declaration under 37 C.F.R. §1.131 demonstrating that he had made the claimed compound before the effective date of the cited prior art reference, even though he had not yet established a utility for that compound. On appeal, the Court indicated that the 131 declaration filed by the patent applicant was sufficient to remove the cited reference. The Court relied on the established "Stempel Doctrine" to support its decision, stating:

> An applicant need **not** be required to show [in a declaration under 37 C.F.R. §1.131] any more acts with regard to the subject matter claimed that can be carried out by one of ordinary skill in the pertinent art following the description contained in the reference ... the determination of a practical utility when one is not obvious need **not** have been accomplished prior to the date of a reference unless the reference also teaches how to use the compound it describes.

In re Moore, 170 USPQ at 267 (emphasis added).

Thus, *In re* Moore confirmed the holding in *In re* Stempel which states that in order to effectively remove a cited reference with a declaration under 37 C.F.R. §1.131, **an applicant need only show that portion of his or her claimed invention that appears in the cited reference**.

As the Examiner noted, Jacobs *et al.* discloses a nucleic acid sequence having 99.8% sequence homology with the entire length of the instant sequence of SEQ ID NO: 386. Although Jacobs includes general statements regarding possible uses of the sequence, no specific examples or experimental data are provided regarding the use of its sequence. Therefore, since Jacobs only

discloses a nucleic acid sequence and general utilities based possibly on sequence homology, Applicants respectfully submit that the provisional application 60/096,960 on which the instant application depends simply needs to show possession of the nucleic acid sequence, and the polypeptide that it encodes, as disclosed in Jacobs, and a sequence homology in order to overcome the 35 U.S.C. §102 rejection.

Applicants respectfully submit that U.S. Provisional Application No. 60/096,960, filed on August 18, 1998, provides the nucleic acid and amino acid sequences of the PRO1312 polypeptide and the homology of the polypeptide with Dayhoff sequences GCINTALPH_1, GIBMUCIA_1, P_R96298, AF001406_1, PVU88874 etc.(see U.S. Provisional Application No. 60/096,960 under the section titled "Full-length PRO1312 Polypeptide"). Applicants further suggest the PRO1312 polypeptide may possess activity typical of at least one of these proteins.

Thus, the U.S. Provisional Application No. 60/096,960, filed on August 18, 1998 discloses sequences designated as SEQ ID NO: 1 and SEQ ID NO: 2, which are identical to SEQ ID NO: 387 and SEQ ID NO: 386, respectively, of the above-identified application. Accordingly, Applicants respectfully submit that the provisional disclosure is commensurate in scope with Jacobs.

Submission of Declaration to provide sequencing date

Further, Applicants respectfully submit a Declaration under 37 C.F.R. §1.131 by Dr. Desnoyers, Dr. Goddard, Dr. Godowski, Dr. Paoni, Dr. Gurney and Dr. Wood that establishes that Applicants had cloned and sequenced the nucleic acid and polypeptide of SEQ ID NO: 386 and 387 respectively, on **May 29, 1998** which is before the prior art date of July 30, 1998 for Jacobs. The consideration of the Declaration is respectfully requested.

Applicants respectfully submit that an executed copy of the Declaration will be submitted to the Examiner shortly.

Consequently, Applicants respectfully submit that Jacobs *et al.* is not prior art under 102(a) since its publication date is after the conception of the invention by the Applicant. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection of Claims 119-123 and 132-138 under 35 U.S.C. §102(a).

Claims 119-123 and 132-138 are rejected under 35 U.S.C. §102(b) as being anticipated by Edwards (WO 99/06439, dated February 11, 1999).

Claims 119-123 and 132-138 are rejected under 35 U.S.C. §102(e) as being anticipated by Edwards (USPN 6,312,922, effective date 8/10/1998).

Initially, in view of the cancellation of claims 132-134, these rejections are moot for these claims. Edwards teaches a shorter EST with 63% overall sequence homology to SEQ ID NO: 386 and does not teach utilities like neonatal heart hypertrophy or chondrocyte redifferentiation. hence, all the claim limitations are not taught by Edwards. Therefore it does not anticipate the instantly claimed invention and this rejection should be withdrawn.

Claims 132-133 are rejected under 35 U.S.C. §102(b) as being anticipated by the 1991 Boehringer Mannheim catalog. Also, Claims 132-134 are further rejected under 35 U.S.C. §102(e) as being anticipated by Studier (USPN 5,407,799, dated 4/18/1995).

In view of the cancellation of claims 132-134, these rejections are moot and should be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-2730P1C67). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: December 23, 2004

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